IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No: 038602/0391

In re patent application of
Gregory PLOWMAN *et al.*
Serial No.: 09/069,228 Group Art Unit: 1642
Filed: April 27, 1998 Examiner: K. CANELLA
For: DIAGNOSIS AND TREATMENT OF ALK-7 RELATED DISORDERS

DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
Washington, D.C. 20231

I, Douglas Clary, hereby declare:

1. I am an inventor of the captioned application. I have worked in the field of Biochemistry and Signal Transduction for eighteen years. I presently hold the position of Associate Director at SUGEN, Inc. I have been employed at SUGEN, Inc. since June 1994. My C.V. is attached as Appendix A.

2. I have read the Examiner's arguments in the Advisory Action dated July 23, 2002 in the above-identified application regarding the Examiner's request for evidence to support a utility of the claimed nucleic acid encoding an ALK-7 polypeptide. This declaration is provided to support the utility of ALK-7.

3. The present application contains results of a survey of gene expression for the ALK7 gene on pages 90-91. ALK7 was found to be primarily expressed in the central nervous system, as far as normal tissues are concerned. However, we found additional evidence that the ALK7 transcript was misexpressed in certain tumor lines (e.g. Calu-6) based on our RNA expression survey. This is indicative of a potential role of ALK7 in promoting tumorigenesis or metastasis. In this regard, subsequent publications have confirmed our observations and extended them. In Jornvall et al., cited previously in our

response and attached here as Appendix B, activation of ALK7 led to the subsequent downstream activation of the ERK MAPK pathway, and activati n of SMAD2 and SMAD3. These experiments were performed in a neuronal cell line, PC12, and led to a neuronal differentiation phenotype. While this result may point to the utility of activation of ALK7 in neurons and neuronal precursors, it does not speak directly to the potential role of ALK7 in carcinogenesis. However, the activation of the MAPK pathway is indicative of a receptor system that can promote tumor growth as disclosed in Sebolt-Leopold, J., 2000, also previously cited and attached here as Appendix C.

4. There are a number of other receptor kinases which are normally expressed in the adult nervous system, but are misexpressed in cancers, and activate the MAPK pathway. For example, the receptor c-ret has been found to be overexpressed and rearranged in a number of cancers, including papillary thyroid tumors (Fluge et al. 2001 - Appendix D) and Multiple Endocrine Neoplasia type 2. Further work has demonstrated its ability to activate the MAPK pathway (Melillo et al., 2001 - Appendix E).

Another example are the neuronal Trk receptors, including TrkA. TrkA was cloned as an oncogene and has been found associated with colon cancer, papillary thyroid cancer, and acute myeloid leukemia (Nakagawara, 2001 - Appendix F). It too activates the MAPK pathway, and can lead to mitogenic effects in carcinoma cells (Descamps et al, 2001 - Appendix G). Thus, in many cases, the misexpression in cancer cells of a normally neuronal-specific receptor, such as ALK7, can lead to activation of the MAPK pathway and promotion of carcinogenesis.

5. As noted above, activation of ALK7 also leads to the downstream activation of SMAD2 and SMAD3. This observation is true, not just in the neuronal cell line, but was demonstrated in a lung epithelial line (Watanabe et al, 1999 - Appendix H). In this paper, activated ALK7 was shown to regulate the nuclear localization and activity of SMAD2. This is relevant to cancer biology, in that SMAD2 has been shown to effect the migration of cancer cells. In fact, in collaboration with the known oncogene activated H-ras, activated SMAD2 was able to promote the metastasis of carcinoma cells (Oft et al., 2002 – Appendix I).

6. Thus two independent signaling pathways, ERK MAPK and SMAD2 / SMAD3, which can promote carcinogenesis have been shown to be activated by ALK7. This underscores our initial findings that overexpression of ALK7 in tumor cell lines can be important for carcinogenesis.

7. I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: _____ Date: 1/29/2003
Douglas Clary, Ph.D.